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Sleep deprivation alters energy homeostasis through non-compensatory alterations in hypothalamic insulin receptors in Wistar rats

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ABSTRACT

Studies have shown a gradual reduction of sleep time in the general population, accompanied by increased food intake, representing a risk for developing obesity, type II diabetes and cardiovascular disease. Rats subjected to paradoxical sleep deprivation (PSD) exhibit feeding and metabolic alterations, both of which are regulated by the communication between peripheral signals and the hypothalamus. This study aimed to investigate the daily change of 96 h of PSD-induced food intake, body weight, blood glucose, plasma insulin and leptin concentrations and the expression of their receptors in the hypothalamus of Wistar rats. Food intake was assessed during the light and dark phases and was progressively increased in sleep-deprived animals, during the light phase. PSD produced body weight loss, particularly on the first day, and decreased plasma insulin and leptin levels, without change in blood glucose levels. Reduced leptin levels were compensated by increased expression of leptin receptors in the hypothalamus, whereas no compensations occurred in insulin receptors. The present results on body weight loss and increased food intake replicate previous studies from our group. The fact that reduced insulin levels did not lead to compensatory changes in hypothalamic insulin receptors, suggests that this hormone may be, at least in part, responsible for PSD-induced dysregulation in energy metabolism.

Introduction

Obesity is a global concern; what once was seen only in rich countries, today is evidenced around the world, with the prevalence doubled between 1980 and 2008, regardless of gender, race and age (World Health Statistics 2012 — World Health Organization). Increased prevalence of obesity has high co-morbidity with cardiovascular disease and type II diabetes, and has been attributed to modern lifestyle, characterized by bad eating habits and less physical activity (Egger and Swinburn, 1997). This lifestyle also seems to have changed the sleep habits of the population, as more people undergo episodes of sleep deprivation, or even chronic voluntary sleep restriction, due to stress, work and even leisure (Broman et al., 1996), affecting not only the total sleep time, but also its architecture and quality (Shechter et al., 2012).

If on one hand, obesity may increase the likelihood to develop sleep apnea (Panossian and Veasey, 2012; Peppard et al., 2000), one of the most prevalent sleep disorders (Tufik et al., 2010; Young et al., 1993), on the other hand, reduction of sleep can increase the risk of obesity and type II diabetes (Patel and Redline, 2004; Van Cauter and Knutson, 2008; Vorona et al., 2005; Xu et al., 2010), establishing a vicious circle. Even individuals displaying naturally occurring short sleep (Taheri et al., 2004) and those submitted to short-term sleep restriction (Spiegel et al., 2004, 1999) exhibit hormonal and metabolic changes, including reduced leptin and increased ghrelin plasma concentrations, prolonged return to baseline cortisol levels at night and higher insulin resistance, that strengthens the impact of inadequate sleep on metabolic homeostasis. Spiegel et al. (2004) reported increased rates of hunger and appetite in subjects submitted to two nights of 4 h of sleep, compared to two subsequent nights of 10 h of sleep. In addition, volunteers sleep-restricted for 14 days (5.5 h in bed) increased their preference for high-carbohydrate foods during the night, compared to 14 days of 8.5 h of sleep (Nedeltcheva et al., 2009).

Similar to what is observed in humans, rats subjected to sleep deprivation also display increased food intake (Galvão et al., 2009; Koban et al., 2008; Martins et al., 2010; Rechtschaffen and Bergmann, 1995). Nevertheless, these animals show intense catabolism (Everson and Wehr, 1993; Hipolide et al., 2006; Suchecki et al., 2003) and energy expenditure, resulting in weight loss during the sleep deprivation period (Koban and Stewart, 2006; Martins et al., 2006; Suchecki et al., 2003). Furthermore, reduced plasma concentrations of anabolic hormones such as insulin (Hipolide et al., 2006), testosterone (Andersen et al., 2004), leptin and growth hormone (Everson and Crowley, 2004; Koban and Swinson, 2005) and increased plasma concentrations of catabolic hormones, such as ACTH, corticosterone, noradrenaline, and glucagon (Galvão et al., 2009; Martins et al., 2010; Suchecki et al., 1998) have been reported.

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Despite this evidence, the central mechanisms involved in the metabolic changes induced by sleep deprivation are not yet fully understood. The hypothalamus is the main regulation *locus* of feeding behavior and energy expenditure (Abizaid and Horvath, 2008) and the neuropeptides and neurotransmitters acting in some hypothalamic nuclei are responsible for inhibiting or stimulating feeding behavior (Beck, 2000; Klok et al., 2007; Lustig, 2001). Regulation of these neuropeptides is made in part by peripheral hormones, such as insulin and leptin, which modulate satiety signals that determine the start and end of food intake and energy balance (Klok et al., 2007; Lustig, 2001; Schwartz et al., 1996).

Thus, the aim of this study was to evaluate the time course of plasma concentrations of insulin and leptin and their hypothalamic receptors, correlating these values with food intake, body weight change and blood glucose, throughout four days of paradoxical sleep deprivation.

Methods

Animals

Male Wistar rats, 90 day-old (n = 112) were obtained from Centro de Desenvolvimento de Modelos Experimentais para Medicina e Biologia (CEDEME) of Universidade Federal de São Paulo (UNIFESP). They were housed in the animal facility of the Department of Psychobiology of UNIFESP in plastic cages (grouped in four/five animals) until the beginning of the experiments. The animals were kept under controlled temperature (21 ± 2 °C) and a 12 h/12 h light/dark cycle (lights on at 7:00 a.m.). All procedures were approved by the Ethics Committee in Research of UNIFESP (CEP: 1372/09).

Groups

Initially the animals were distributed into two groups: control (CTL — n = 56) and paradoxical sleep deprivation (PSD — n = 56). Each of these groups was then subdivided equally into four new groups, according to the day of euthanasia: CTLD1, CTLD2, CTLD3, CTLD4, PSDD1, PSDD2, PSDD3 and PSDD4. Each group was composed of 14 animals.

Paradoxical sleep deprivation

Animals were submitted to PSD by the single platform technique, by housing them in water containers (22 cm long × 22 cm wide × 35 cm high) onto a platform 6.5 to 7.0 cm in diameter. The platform remained immersed in water up to 1.0 cm from its upper surface. Control animals were housed in similar containers lined with corn cob. For each container, water and food were provided ad libitum in removable compartments. The animals were habituated to the sleep deprivation facility for two weeks and to the experimental environment for 60 min/day during the three days before the beginning of the experiments. The protocol of PSD lasted 96 h.

Assessment of body weight and food consumption

All animals underwent this evaluation. Body weights were recorded daily in the morning (7:30 a.m.) after we made sure that the animals were not wet, from the adaptation period until the last day of PSD. Since we sought to determine the daily changes induced by PSD, the percent weight change was calculated by the following equation: [(current weight − previous weight) / previous weight] × 100. For determination of food intake, chow pellets were weighed daily at two different times: at 7:00 a.m., to assess intake during the dark phase, and at 7:00 p.m., to assess food intake during the light phase.

Measurements of glucose, insulin and leptin

Half of the animals in each group (n = 7/group/day) was used for biochemical receptor expression assessment. The animals were euthanized by decapitation (9:00 a.m.), 2 h after removal of the food containers for the purpose of reducing the variability of results. One drop of blood was used to determine glucose levels by OneTouch™ device Johnson & Johnson (system measuring range: 20 to 600 mg/dL). Trunk blood was also collected in dry tubes containing 0.1 mL of a 6% EDTA solution and centrifuged at 2400 rpm for 20 min at 4 °C. Plasma was stored in two separate aliquots and frozen (−20 °C) for later determination of hormone concentrations. Insulin and leptin levels were determined by radioimmunoassay (Millipore EMD Chemicals, Germany). The sensitivity of the insulin assay is 0.081 ng/mL; intra- and inter-assay variabilities of 1.4 to 4.6% and 8.5 to 9.4%, respectively. The sensitivity of the leptin assay is 0.639 ng/mL, intra-assay variability of 2.8 to 3.6% and inter-assay variability of 6.5 to 8.7%.

Expression of insulin and leptin receptors in the hypothalamus

After decapitation, the brains were removed from the skull and the hypothalamus was dissected, frozen and stored at −80 °C for posterior Western blotting assays. The total cell lysates of the hypothalamus were homogenized in lysis buffer (T-PER Tissue Protein Extraction Reagent, Thermo Scientific, USA and protease and phosphatase inhibitors cocktails, Pierce, USA) and total protein concentration was determined by Lowry's method (Lowry et al., 1951). The samples were subjected to electrophoresis on SDS-polyacrylamide gel. The separating gel of 10% polyacrylamide was prepared in 0.4 M Tris–HCl buffer (pH 8.8), containing 0.1% SDS, 0.01% N, N, N′, N′-tetra metiletilenodiamina (TEMED) and 0.05% ammonium persulfate. After polymerization of the gel, the stacking gel was prepared containing 3% polyacrylamide in 0.1 M Tris–HCl buffer (pH 6.8), 0.1% SDS, 0.01% TEMED and 0.05% ammonium persulfate. An aliquot of 50 μg of total protein hypothalamic extract was combined with denaturant and reductant buffer containing 0.125 M Tris–HCl (pH 6.8), 4% SDS, 20% glycerol, 0.002% bromophenol blue and 4% mercaptoethanol. Samples were heated at 95 °C for 5 min and applied on the gel. 0.025 M Tris–HCl, containing 0.18 M glycine, pH 8.3, and 1% SDS, was used as a running buffer. The runs were performed at 100 V for 2.5 h at room temperature. Then the samples were transferred by electroblotting to nitrocellulose membrane (Amersham GE, Little Chalfont, UK). The membranes were blocked with 2% non-fat milk for 2 h and then incubated with primary antibodies overnight at the indicated dilutions: rabbit anti-insulin receptor Santa Cruz Biotechnology (Santa Cruz, CA, USA) 1:1000 and rabbit anti-LepRb (Abcam, Cambridge, UK) 1:2000, respectively. After three washes of 5 min, the membranes were incubated for 45 min with Alexa-680-conjugated anti-rabbit IgG (1:10,000, Invitrogen, Carlsbad, CA, USA). After five washes of 5 min, digital images of the membranes were acquired and quantified, by pixel density, using the Odyssey Infrared Image System (LI-COR, Baltimore, MD, USA).

Statistical analysis

Statistical analysis of daily food intake was performed by the General Linear Model (GLM) for repeated measures, with Group (CTL, PSD), Day (D1, D2, D3, D4 — repeated measures) and Phase (light, dark — repeated measures) as main factors. Analysis of body weight was carried out by GLM for repeated measures with Group (CTL, PSD) and Day (D1, D2, D3, D4 — repeated measures) as main factors. GLM univariate test was applied to blood glucose, plasma insulin and leptin levels, and expression of insulin and leptin receptors, with main factors: Group (CTL, PSD) and Day (D1, D2, D3, D4). When required, Bonferroni post hoc test was used, and the significance level was established at $p < 0.05$. Finally, Pearson's correlation test was applied to evaluate the

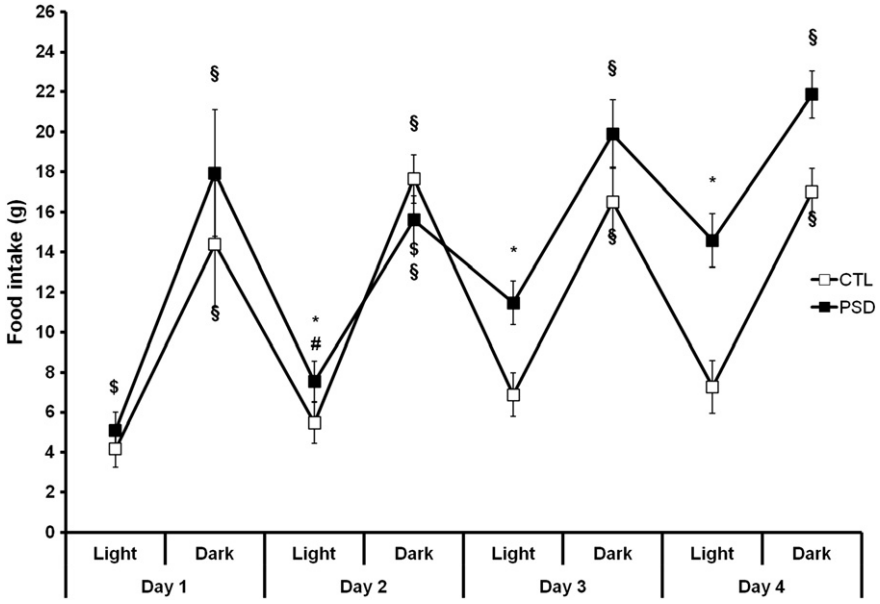


Fig. 1. Effect of four days of PSD on food intake (mean ± SEM). Chow pellets were weighed daily during the light (07:00 a.m. to 07:00 p.m.) and dark phases (07:00 p.m. to 07:00 a.m.) of the day cycle. * different from the CTL group; § different from the light phase; $ different from days 3 and 4; # difference from day 4; p's < 0.003; n = 28 (CTL = 14 / PSD = 14).

correlations between insulin, leptin, food intake, body weight and blood glucose levels.

Results

Food intake

GLM revealed a main effect of Group ($F_{1,26} = 14.69$; $p < 0.001$), Day ($F_{3,78} = 27.96$; $p < 0.001$), Phase ($F_{1,26} = 247.61$; $p < 0.001$) and interactions Group × Day ($F_{3,78} = 7.65$; $p < 0.001$) and Group × Phase ($F_{1,26} = 4.92$; $p < 0.05$) (Fig. 1). Post hoc analysis showed that food intake during the dark phase was always higher than during the light phase; group comparisons showed that PSD rats consumed more food than CTL ones in the light phase of days 2, 3 and 4 (p's < 0.003). However, during the dark phase, the food intake of PSD rats was significantly lower on day 2 than on days 3 and 4 (p's < 0.003). During the light phase, the food intake of PSD rats was higher on days 3 and 4 than on day 1 (p's < 0.003), and on day 4 compared to day 2 ($p < 0.05$).

Body weight

GLM showed a main effect of Group ($F_{1,26} = 86.10$; $p < 0.001$), Day ($F_{3,78} = 36.12$; $p < 0.001$) and an interaction between Group × Day ($F_{3,78} = 5.52$; $p < 0.05$) (Fig. 2). Post hoc analysis revealed greatest body weight loss on day 1 for both groups (p's < 0.006). In addition, PSD rats lost more body weight on days 1 and 2 than the CTL group (p's < 0.006).

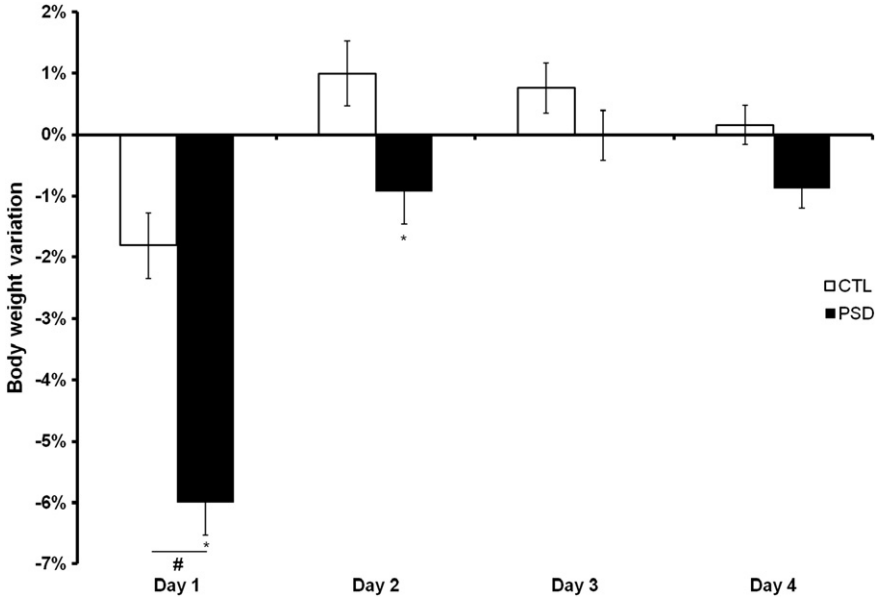
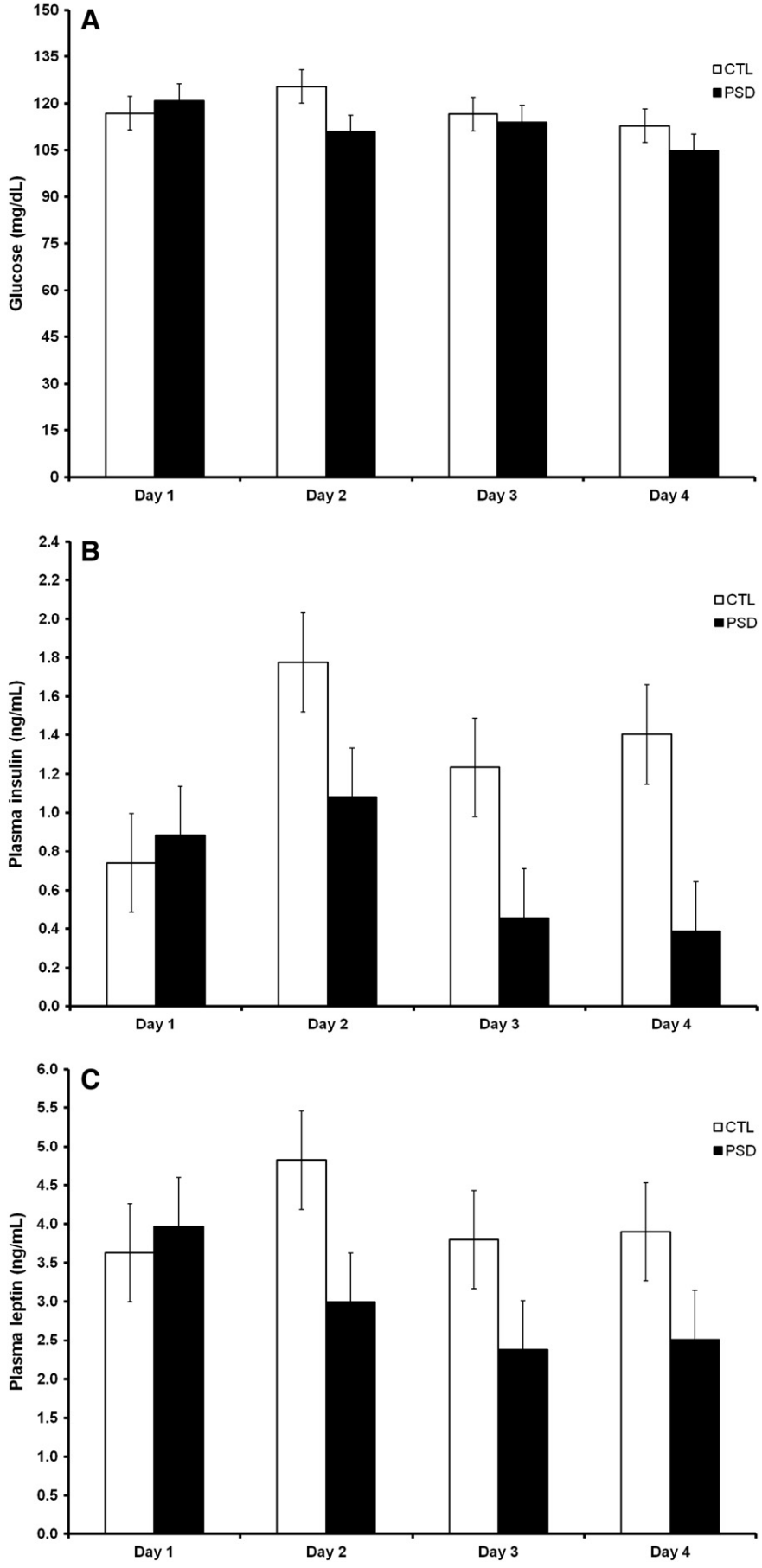


Fig. 2. Effect of four days of PSD on body weight (mean ± SEM). Body weight was recorded at 7:30 a.m. and the percent weight change was calculated by the following equation: [(current weight − previous weight) / previous weight] × 100. * different from the CTL group; ¥ different from days 2, 3 and 4; p's < 0.006; n = 28 (CTL = 14 / PSD = 14).


A
Glucose (mg/dL)
150
135
120
105
90
75
60
45
30
15
0
CTL
PSD
Day 1
Day 2
Day 3
Day 4
B
Plasma insulin (ng/mL)
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
CTL
PSD
Day 1
Day 2
Day 3
Day 4
C
Plasma leptin (ng/mL)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
CTL
PSD
Day 1
Day 2
Day 3
Day 4

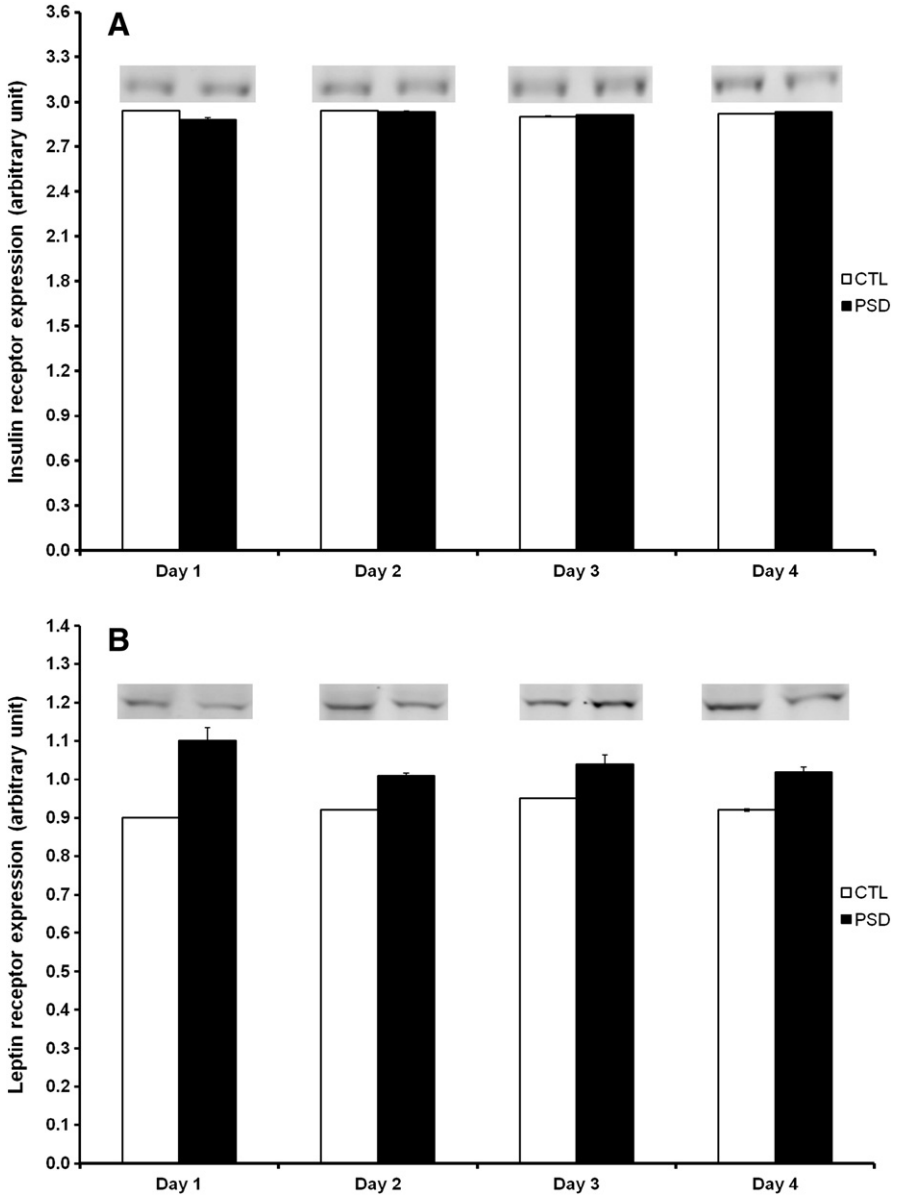


Fig. 4. Effect of four days of PSD on the expression of hypothalamic insulin (A) and leptin (B) receptors (mean ± SEM). The total cell lysates of the hypothalamus were homogenized and the expression of receptors was determined by Western blotting. For leptin, the GLM revealed a main effect of group; $p < 0.05$; $n = 8$ (CTL = 4 / PSD = 4).

Glucose, insulin and leptin

Analysis of daily glucose levels (Fig. 3A) revealed no effect for any of the factors (Group and Day). Conversely, GLM analysis of daily insulin secretion (Fig. 3B) showed a main effect of Group ($F_{1,48} = 10.61$; $p < 0.05$) and PSD rats displayed lower levels than the CTL group ($p < 0.05$). Finally, for leptin (Fig. 3C), GLM revealed a main effect of Group ($F_{1,48} = 5.77$; $p < 0.05$). As seen for insulin, PSD had significantly lower leptin levels than the CTL group ($p < 0.05$).

Expression of insulin and leptin receptors in the hypothalamus

There were no significant differences in the expression of insulin receptors between groups ($F_{3,24} = 0.30$; $p = 0.59$; Fig. 4A), nor throughout the protocol of sleep deprivation ($F_{3,24} = 0.41$; $p = 0.74$). GLM revealed a main effect of Group ($F_{1,24} = 8.55$; $p < 0.01$) on leptin receptors (Fig. 4B), with significantly higher expression of hypothalamic leptin receptors in PSD than in the CTL group ($p < 0.01$).

Correlations

Positive correlations were observed during the four days of PSD between insulin × leptin plasma levels (Fig. 5A) ($r = 0.4234$; $p < 0.001$), insulin levels × body weight (Fig. 5B) ($r = 0.4999$; $p < 0.001$) and leptin levels × body weight (Fig. 5C) ($r = 0.3845$; $p < 0.01$).

Discussion

This study showed that PSD increased food intake only during the light phase; it also induced weight loss, mainly in the first day, a

Fig. 3. Effect of four days of PSD on daily glucose (A), insulin (B), and leptin levels (C) (mean ± SEM). Blood glucose concentrations were determined 2 h after removal of food containers (at 9:00 a.m.). Blood sampling was obtained by decapitation and insulin and leptin levels were determined by radioimmunoassay. For insulin and leptin, the GLM revealed a main effect of Group; p's < 0.05; n = 14 (CTL = 7 / PSD = 7).

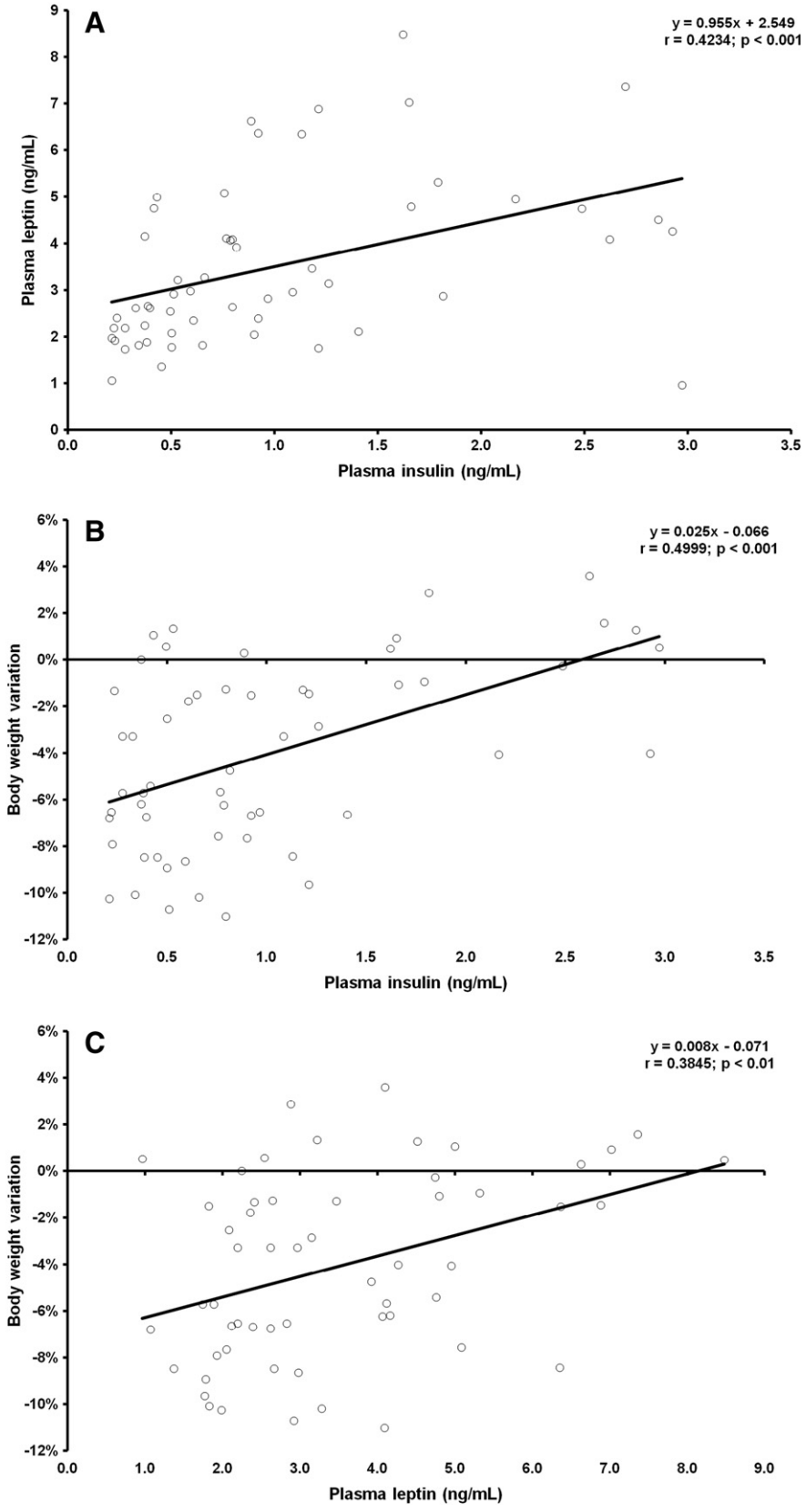


Fig. 5. Correlation between insulin × leptin levels (A), insulin levels × variation in body weight (B) and leptin levels × variation in body weight (C). N = 56 (CTL = 28 / PSD = 28).

decrease in insulin and leptin plasma concentrations and increased expression of hypothalamic leptin, but not of insulin, receptors.

Although PSD-induced weight loss is a consensus among numerous laboratories (Kushida et al., 1989; Elomaa, 1981; Coenen and Van Luijtelaar, 1985; Suchecki and Tufik, 2000; Martins et al., 2006; Koban and Swinson, 2005), its effect on food intake is still a matter of debate. Some studies find no changes (Elomaa, 1981; Martins et al., 2006), whereas others report increased food intake, regardless of differences

in length of deprivation or type of diet offered this period (Kushida et al., 1989; Koban et al., 2008; Martins et al., 2011). This discrepancy can be partly explained by excessive waste of food pellets in the water during PSD (Martins et al., 2006), which, in some studies, were not deducted from the amount of food measured. This increased loss of food is due to PSD-induced stereotyped gnawing behavior, resulting in overestimation of the ingested chow by the animals (Martins et al., 2008). Another possible explanation for the inconsistency in food intake among laboratories may be due to the fact that measurement is accomplished once/day, and does not reflect possible differences between phases of the light–dark cycle. Galvão et al. (2009) found an increase in food intake during the light phase of the circadian rhythm in animals paradoxical sleep-deprived for four days after correcting for food spillage. In the present study, food waste was not measured during assessment of food intake; nonetheless, by applying the correction factors proposed by Galvão et al. (2009), we observed the same significant differences. Thus, the present data corroborated previous findings from our group (Galvão et al., 2009), with rats showing a progressive increase of food intake only during the light phase. These results suggest that even short periods of PSD are able to change the feeding behavior profile of the animals. In fact, there is an increased immunoreactivity of orexin in the lateral hypothalamus at the end of 96 h of PSD (Galvão et al., 2009) and increased mRNA for the translation of orexin begins after 24 h of PSD onset, preceding other orexigenic neuropeptides such as neuropeptide Y (Martins et al., 2010). Moreover, cerebrospinal fluid orexin levels are increased by 96 h of paradoxical sleep deprivation, when samples are collected 8 h (ZT8), but not immediately (ZT0), after lights on. The lack of effect of PSD at ZT0 may be explained by a ceiling effect on orexin levels at this time-point (Pedrazzoli et al., 2004).

As for the animals' body weight, our results are consistent with previous findings in the literature, showing the unequivocal weight loss (Everson and Crowley, 2004; Koban and Stewart, 2006; Martins et al., 2006; Suchecki et al., 2003), particularly in the first day of PSD. This weight loss is directly related to the intense state of catabolism displayed by these animals, which present a negative energy balance, with greater energy expenditure (Bergmann et al., 1989; Hipolide et al., 2006), increased oxygen consumption and expression of uncoupling protein-1 in brown adipose tissue (Koban and Swinson, 2005), increased catecholamine (Andersen et al., 2005) and reduced body fat (Hipolide et al., 2006), also coinciding with the peak release of corticosterone (Galvão et al., 2009), an important catabolic hormone.

Previous studies of total sleep restriction report reduction of blood glucose levels but without changes in food intake (Barf et al., 2012; Vetrivelan et al., 2012). In our study, no changes in blood glucose were observed, confirming previous findings (Martins et al., 2010; Suchecki et al., 2003), although PSD rats showed negative energy balance. This result suggest that PSD induces such high energetic demand, that even reduction of insulin plasma levels and lack of compensatory regulation of the hypothalamic insulin receptors does not lead to increased blood glucose levels. Therefore, animals utilize all kinds of energetic sources, such as raise in regular chow, glucose solution (Suchecki et al., 2003) and hyperlipidic diet (Everson and Wehr, 1993). It is possible, therefore, to propose that increased food intake during paradoxical sleep deprivation functions to counterbalance the negative energy balance, minimizing the impact of deprivation on blood glucose.

PSD reduced plasma levels of leptin and insulin from the second day on, with the lowest values being reached at the end of the last day of deprivation. These results are consistent with data from the literature showing decreased concentrations of insulin (Hipolide et al., 2006) and leptin (Koban and Swinson, 2005), and increased glucagon levels (Martins et al., 2010) in animals submitted to PSD. These changes contribute to catabolism and suggest that the longer the length of PSD the lower these hormones plasma concentrations. Indeed, insulin and leptin are major adiposity signals (Woods and Seeley, 2000), e.g., they are directly related to body fat and they regulate food intake and energy homeostasis by acting on the central nervous system (CNS) (Schwartz et al., 1999; Woods et al., 1998). Thus, the binding of these two hormones to their receptors in the hypothalamus reduces food intake, and increases energy expenditure and body weight loss (Air et al., 2002; Brown et al., 2006; McGowan et al., 1992, 1990; Seeley et al., 1996). The results of correlation between body weight and plasma levels of these hormones are in agreement with the abovementioned studies.

Insulin and leptin receptors are widely distributed in the CNS (Fei et al., 1997; LeRoith et al., 1988), although the highest levels are found in hypothalamic neurons, mainly in the arcuate nucleus (ARC) (Baskin et al., 1999; Woods and Seeley, 2000). Neurons in the ARC synthesize and release neuropeptides responsible for both stimulation (Orexin, Neuropeptide Y, Agouti-related peptide) and inhibition of feeding behavior (Corticotropin-releasing hormone, Pro-opiomelanocortin) (Schwartz et al., 2000) and project to important hypothalamic areas involved in the control of energy homeostasis such as the paraventricular nucleus and the lateral hypothalamus (Elmquist et al., 1999, 1998). Synthesis and release of these neuropeptides are under control of peripheral signals of energy stores (leptin, insulin and ghrelin). Thus, PSD most likely led to increased expression of hypothalamic leptin receptors as a compensatory response to reduced leptin plasma levels and increased production of orexigenic neuropeptides (Galvão et al., 2009; Martins et al., 2010), in an attempt to maintain energy homeostasis. Knock out of leptin (Balthasar et al., 2004; Van de Wall et al., 2008), but not insulin (Konner et al., 2007), receptors in ARC neurons produces hyperphagia and increased body weight. The lack of change in insulin receptors throughout PSD may be related to the fact that blood glucose in sleep-deprived animals was, somehow, kept stable. Importantly, the action of insulin in the CNS is related to acute changes in glucose concentration and metabolism, unlike leptin, which has a broader action on energy balance and is more directly linked to fat mass (Woods and Seeley, 2000).

The present results are in line with some of the metabolic changes induced by sleep deprivation in humans, such as increased food intake and reduced leptin and insulin plasma levels. Interestingly, hypothalamic leptin receptors were upregulated on the first PSD day and this compensatory regulation may be associated with the control of energy balance during PSD. Conversely, the lack of compensatory change in insulin receptors most likely led to impaired insulin signaling, which could be involved in dysregulation of food intake. Based on the present results, we propose that the compensatory change in leptin receptors is important to maintain energy balance, whereas disruption of the insulin signaling is involved in dysregulation of the feeding behavior during PSD, that could serve the purpose of fulfilling the high energetic demand imposed by this condition.

Acknowledgments

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